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Prediction of long-term ischemic stroke with estimated whole blood viscosity in heart failure patients

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ABSTRACT

Aims: Heart failure (HF) and stroke often coexist and share common risk factors, including atrial fibrillation. Whole blood viscosity (WBV), one of the most significant indicators of endothelial stress, is a fundamental determinant of blood flow and is involved in the aetiology of atherosclerosis and thrombosis. The purpose of this study was to assess the association between estimated WBV and long-term ischemic stroke (IS) risk in patients hospitalized for acute HF.

Methods: A total of 409 patients with reduced ejection fraction HF hospitalized with acute HF were included. The primary outcome was IS post-discharge follow-up.

Results: IS occurred in 26 (6%) patients during a follow-up. In the IS group, older age, diabetes mellitus frequency and WBV were higher, left ventricular end-diastolic and left atrial anteroposterior diameter were increased and left ventricular ejection fraction was lower. In multivariate regression analysis, WBV was found to be a predictor of long-term IS (OR, 2.68; 95% CI, 1.96-3.12, p=0.008). In the receiver operating characteristic curve, the optimal cut-off value of WBV for one-year IS was 6.28 with 61.5% sensitivity and 70.2% specificity (area under the curve: 0.748).

Conclusion: WBV is a novel, easily measurable, cost-effective, non-invasive risk marker for the prediction of long-term IS in patients with HF, independent of traditional risk factors.

Keywords: Heart failure, ischemic stroke, whole blood viscosity

Our research's data was presented in 2nd National Heart Failure Congress as 'Oral Presentation' on June 2023.

INTRODUCTION

Heart failure (HF) is a rapidly growing global public health concern that affects almost millions of individuals globally and is a leading cause of mortality and re-hospitalization.[1] Moreover, stroke is the leading cause of death and disability worldwide after ischemic heart disease.[2] HF prognosis is significantly impacted by comorbidities related to HF.[1,3,4] Owing to its enormous prevalence, HF may significantly influence the occurrence of other illnesses, such stroke.[2-4] HF and stroke often coexist and share common etiological risk factors, including atrial fibrillation (AF).[1-4] Because of the increased activity of pro-coagulant factors and thromboembolic consequences, HF may raise the risk of an ischemic stroke (IS).[2-4] On the other hand, HF is commonly together with low blood pressure, which may prevent IS.[1,3-5] It have been still unknown whether HF directly causes the increased risk of IS, despite the fact that patients with HF had a two to three times greater risk of IS than general population.[3-7] This is due to the fact that the majority of stroke research with HF population does not accurately account for confounding factors or distinguish between patients with and without AF.[2,4-8] It is well known that current guidelines recommend the use of the CHA_2DS_2-VASc score to evaluate IS risk in HF patients with AF.[3,4] Anticoagulant treatment is indicated with a class I recommendation in cases with a CHA_2DS_2-VASc score ≥2.[3,4] Although some observational study data have been presented to determine stroke risk in HF patients without AF, anticoagulant or antiagregant treatment management has not been finalized.[5-10] In HF patients without AF, supportive parameters are needed to predict stroke risk and appropriate treatment management. Whole blood viscosity (WBV), one of the significant determinants of endothelial stress, was a strong parameter of blood flow and was revealed to involved in atherosclerosis and thrombosis.[11-13] Numerous studies have previously shown the association between elevated whole blood viscosity and adverse clinical outcomes, such as mortality, as well as its prognostic significance in cardiovascular diseases.[12-16]

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Because of significant role of WBV in the prediction of thrombogenicity and the uncertainty of research on stroke in HF patients, we aimed to evaluate the association between estimated WBV and long-term IS risk in patients hospitalized for acute HF.

METHODS

Ethics

The study was initiated with the approval of the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 24.08.2022, Decision No: 266). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population and Design

In this retrospective observational research, 485 patients who applied to our center with HF symptoms between March 2020 and March 2023 were evaluated as New York Heart Association (NYHA) class 2-4 and were hospitalized for acute HF with reduced ejection fraction (HFrEF) were included. Those who satisfied at least one of the following criteria were excluded; diagnosis of with left ventricular (LV) thrombus and AF (n=20), receiving anticoagulant treatment (n=24), haemorrhagic stroke (n=5), active kidney infection, nephrotic syndrome or chronic kidney disease under hemodialysis treatment (n=10), active cancer (n=3), autoimmune disease (n=3), severe liver disease (n=6), hypo- or hyperthyroidism (n=5) (**Figure 1**). Following exclusion, 409 patients were included in final analysis. The hospital's medical database provided demographic, laboratory, and clinical data. Furthermore, telephone interviews or the national health registration system were used to collect follow-up data.

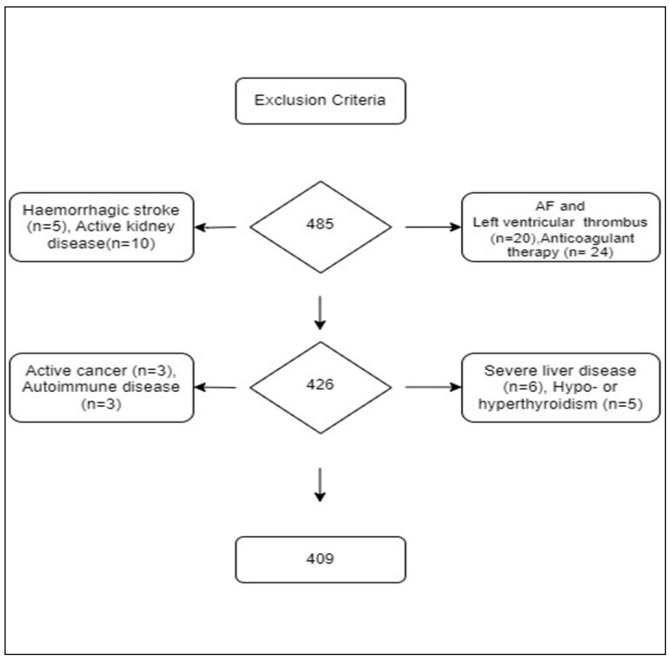
Exclusion Criteria
Haemorrhagic stroke (n=5), Active kidney disease(n=10)
485
AF and Left ventricular thrombus (n=20),Anticoagulant therapy (n= 24)
Active cancer (n=3), Autoimmune disease (n=3)
426
Severe liver disease (n=6), Hypo- or hyperthyroidism (n=5)
409

Figure 1. A flow chart for study inclusion and exclusion criteria

Definitions and Risk Factors

HFrEF was defined as the presence of symptoms or signs of HF and evidence of cardiac dysfunction: either LV ejection fraction (LVEF) <40% or increased plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>125 ng/l).[3,4] HF with a history of myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery, as well as stenosis of greater than 70% in any vessel or more than 50% in the left main coronary artery, was desribed as ischemic cardiomyopathy.[3,4] Baseline laboratory parameters were meticulously documented for each patient during the emergency admission, encompassing a comprehensive set of analyses Assessments of complete blood counts were performed with the Beckman Coulter LH 750 device, which is situated in Fullerton, California, in the United States. The Cobas C7001 equipment from Roche Diagnostics in Rotkreuz, Switzerland was used to assess the lipid profile and other biochemical variables. According to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), patients were classified as having diabetes mellitus (DM), hypertension (HT), or hyperlipidemia if any of those disorders had been detected.[17] The formula for calculating body mass index (BMI) is weight in kilograms divided by height in meters squared (kg/m²). Smoking status was determined by considering a participant a current smoker if they were consistently smoking or had smoked in the 1 month leading up to the study. AF was diagnosed as the absence of irregular R-R interval and P-wave on hospitalization or follow-up electrocardiograms (ECGs).[18] Moreover, all patients had at least one 48-hour rhythm holter monitoring during a follow-up of approximately one year. Patients with a narrow QRS, irregular R-R interval of more than 30s, and irregular R-R interval on rhythm holter monitoring were considered to have AF.[18] A stroke was defined as a focal neurological deficit that was induced by a non-traumatic event and lasted for at least 24 hours.[19] It was categorized as either an ischemic, hemorrhagic, or undetermined type stroke based on the results of computed tomography or magnetic resonance imaging.[19]

WBV was calculated by the De Simone formula, which is rapid and simple to assess [WBV(s) (208 s-1)=(0.12×HCT)+0.17 (total protein-2.07)].[11] Following the recommendations of the American Society of Echocardiography, licensed cardiologists conducted echocardiographic assessments on participants using a Hitachi ultrasound cardiovascular system (Arietta 65, USA) with a 2.5-3.5 MHz transducer, without knowledge of any clinical data.[20] The modified biplane Simpson's rules were used to measure LVEF.

Follow up and Outcomes

The patients were monitored for a median of 15 (11-21) months. The primary outcome was IS post-discharge follow-up.

Statistical Analysis

The data were reported as median [interquartile range (IQR)] for continuous variables and as percentages (n) for categorical variables. The Kolmogorov-Smirnov test was used to determine if the continuous variable distribution was normally distributed. IS was the basis for stratifying the participants into two groups. The Mann-Whitney U-test was utilized to compare non-normally distributed continuous variables, and the Pearson Chi-square test was applied to evaluate the frequency of categorical variables across these groups. Both univariate and multivariate regression analyses included parameters that had significant differences between the two groups. The receiver operating characteristics curve (ROC) analysis was then used to evaluate the predictive performance of estimated WBV. For every analysis, a 95% confidence interval was taken into account and a significance level of $p<0.05$ was adopted. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was utilized for these statistical analyses.

RESULTS

Baseline Characteristics

The total study population included 409 patients with a median age of 55 years (IQR: 47-63) years, 55 (72.4%) of whom were male. IS was observed in 6% of patients with HFrEF during a median follow-up period of 15 months. The IS (+) group had a higher median age than the IS (-) group [65 (60-71) vs 54 (46-63), $p<0.001$. Similarly, IS (+) group exhibited a statistically higher incidence of DM ($p=0.001$), left atrial anteroposterior diameter (LA-APD) ($p<0.001$), LV end-diastolic diameter (LVDD) ($p=0.009$), and LVEF ($p=0.001$). Male gender, HT, COPD, smoking and BMI were, on the other hand, comparable between the groups. In addition, IS (+) group had lower hemoglobin ($p=0.004$) and total protein levels ($p=0.025$). A total of 177 (43%) patients were on single antiplatelet therapy and 75 (18%) were on dual antiplatelet therapy. Table 1 provided comprehensive clinical, laboratory, and demographic characteristics of the research cohort which reported according to IS.

Independent Predictors of IS

Univariate analysis presented that age, DM, LA-APD, LVDD, LVEF and WBV were significantly associated with IS (respectively, age: OR, 1.09; 95% CI, 1.08 – 1.13, $p<0.001$; DM: OR, 3.63; 95% CI, 1.62-4.55, $p=0.002$; LA-APD: OR, 1.10; 95% CI, 1.03-1.17, $p=0.002$, LVDD: OR, 1.04; 95% CI, 1.07-1.08 $p=0.019$ and LVEF: OR, 0.91; 95% CI, 0.85-0.96, $p=0.003$) (Table 2). The WBV remained an independent predictor of IS even after several risk factors, including significant clinical variables in the univariate model, were included in the multivariate model for adjustment (OR: 2.68, 95% CI 1.96-3.12, $p=0.008$) (Table 2).

Diagnostic Performance of WBV for IS

The ability of WBV levels to predict IS was evaluated using ROC analysis. Figure 2 indicated that WBV had a respectable capacity to predict an IS (AUC: 0.748, $p<0.001$) according to the findings of the ROC analysis. The WBV cut-off value was found to be 6.28, resulting in a 61.5% sensitivity and a 70.2% specificity.

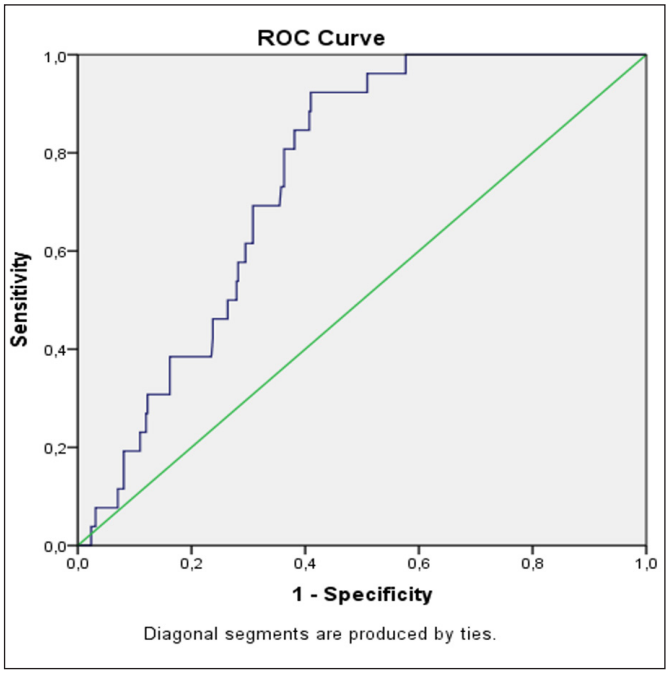

Figure 2. Receiver operating characteristic (ROC) curve analysis of total blood viscosity for ischemic stroke prediction (AUC:0.748 , Cut 6.28 , sensitivite 61.5% spesifite 70.2%)

DISCUSSION

There is a host of variables linked to stroke and other unfavorable outcomes in patients with HFrEF. These variables are grouped around treatment modalities, clinical characteristics, and laboratory parameters. We identified that DM, LA-APD, LVEF and WBV were independent predictors of IS prediction in patients with HFrEF. This was the first study to assess the association between WBV and the likelihood of a IS in HFrEF patients. The results of this investigation proved and verified that the elevated WBV values measured by De Simone formula were an independent, consistent measure of long- term IS prediction, regardless of other parameters in patients with HFrEF.

Table 1. Baseline characteristics of the study population

Variables	Overall (n= 409)	IS (-) (n=383)	IS (+) (n=26)	p-value*
Demographic features and risk factors				
Age, years; median, (IQR)	55 (47-63)	54 (46-63)	65 (60-71)	<0.001
Male; n (%)	332 (81.2)	309 (80.7)	23 (88.5)	0.326
DM; n (%)	107 (26.2)	93 (24.3)	14 (53.8)	0.001
HT; n (%)	181 (44.3)	165 (43.1)	16 (61.5)	0.067
HL; n (%)	102 (24.9)	94 (24.5)	8 (30.8)	0.699
Smoking; n (%)	109 (26.7)	101 (26.4)	8 (30.8)	0.624
Ischemic heart failure; n (%)	240 (58.7)	225 (58.7)	15 (57.7)	0.916
COPD; n (%)	43 (10.5)	41(10.7)	2 (7.7)	0.628
BMI; mean±SD	27±4.1	26.9±4.1	28±5.8	0.230
WBV; median (IQR)	5.9 (5.3- 6.3)	5.7 (5.2-6.3)	6.3 (6.1-6.6)	<0.001
LVDD, mm; median (IQR)	62 (56-67)	61 (56-66)	66 (59-74)	0.009
LA-APD, mm; median (IQR)	46 (42-49)	45 (42-49)	49 (47-52)	<0.001
LVEF, %; median (IQR)	30 (25-30)	30 (25-35)	26 (26-30)	0.001
Laboratory measurements				
Total cholesterol, mg/dl; median (IQR)	169 (146-188)	169 (145-188)	174 (153-189)	0.355
Trigliserid, mg/dl; median (IQR)	113 (92-140)	113 (92-140)	112 (88-134)	0.673
HDL-C, mg/dl; median (IQR)	35 (30-40)	35 (30-40)	37 (31-40)	0.571
LDL-C, mg/dl; median (IQR)	107 (87-120)	106 (87-120)	112 (97-135)	0.092
Creatinine, mg/dl; median (IQR)	1.03 (0.84-1.26)	1.01 (0.83-1.25)	1.1 (1.00-1.30)	0.076
BUN, mg/dl; median (IQR)	21 (16-29)	21 (16-29)	23 (16-32)	0.371
Glucose, mg/dl; median (IQR)	108 (92-141)	108 (92-142)	97 (89-120)	0.088
WBC count, 10^3/µl; median (IQR)	8.2 (6.9-10.1)	8.3 (6.9-10.1)	8 (6.8-10.4)	0.714
Hemoglobin, mg/dl; median (IQR)	13.1 (11.3-14.4)	13 (11.3-14.3)	13.6 (13.4-14.6)	0.004
Platelet count, 10^3/µl; median (IQR)	228 (196-292)	230 (196-292)	217 (195-315)	0.790
Lymphocyte count, 10^3/µl; mean±SD	2.1±0.93	2.09±0.32	2.3±1.17	0.342
Neutrophil count, 10^3/µl; mean±SD	5.4±2.22	5.4±2.25	5.4±1.79	0.478
CRP, mg/L; median (IQR)	0.9 (0.2-3.7)	0.9 (0.2-3.7)	1.0 (0.3-2.7)	0.885
Total protein, g/dl; mean±SD	7.3±2.4	7.3±2.4	8.4±1.07	0.025
Albumin, g/dl; mean±SD	3.9±1.4	3.9±1.4	4.1±0.49	0.140
Sodium, mEq/L; mean±SD	136 ±7.5	138±7.7	138±3.3	0.408
Potassium, mmol/L; median (IQR)	4.3 (4-4.6)	4.3 (4.0-4.7)	4.2 (4.8-4.4)	0.331
Magnesium, mg/dl; mean±SD	2±0.31	2±0.32	1.9±0.17	0.390
Calcium, mg/dl; median (IQR)	9.1 (8.7-9.6)	9.1 (8.7-9.6)	9.2 (8.7-9.5)	0.673
NT-proBNP, pg/ml; median (IQR)	925 (502-1816)	925 (511-1815)	960 (364-1862)	0.724
Medications prescribed before admission				
CCB; n (%)	34 (8.3)	32 (8.4)	2 (7.7)	0.903
B-blocker; n (%)	386 (94.6)	362 (94.8)	24 (92.3)	0.592
Antiaggregan; n (%)	252 (61.6)	234 (61.0)	18 (69.2)	0.585
ACE-I /ARB/ARNI, n (%)	341 (83.6)	319 (83.5)	22 (84.6)	0.883
MRA; n (%)	197 (48.3)	185 (48.4)	12 (46.2)	0.822
Thiazide; n (%)	73 (17.9)	66 (17.3)	7 (26.9)	0.214
Statin; n (%)	132 (32.4)	125 (32,7)	7 (26.9)	0.541

p<0.05 was considered statistical significance. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker;ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; BUN, blood urea nitrogen; CPOD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; HL, hyperlipidemia; IQR, inter quartil range; IS, ischemic stroke; NT-proBNP, N-terminal pro b-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; LA-APD, left atrium antero-posterior diameter; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; mm, millimeter; MRA, mineralocorticoid receptor antagonist; SD, standart deviation; WBC, white blood cell; WBW, whole blood viscosity

Table 2. Univariate and multivariate regression analysis for prediction ischemic stroke

Variable	Univariate Analysis			Multivariate Analysis		
	OR	CI (95%)	p value*	OR	CI (95%)	p value*
Age, years	1.09	1.08-1.13	<0.001	1.12	1.02-2.52	<0.001
LVEF, %	0.91	0.85-0.96	0.003	0.927	0.89-0.98	0.048
LVDD, mm	1.04	1.07-1.08	0.019	1.03	0.983-1.09	0.187
LA –APD, mm	1.10	1.03-1.17	0.002	1.14	1.12-1.67	0.006
DM	3.63	1.62-4.55	0.002	1.55	1.25-2.24	0.010
WBV	2.11	1.24-3.60	0.006	2.68	1.96-3.12	0.008

DM, diabetes mellitus; LA-APD, left atrium antero-posterior diameter; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; mm, millimeter; WBW, whole blood viscosity

Compared to most malignancies, HF has a higher death and morbidity rate.[1] Consequently, managing HF patients is critical to lowering the medical, social, and financial burdens associated with their condition.[1,3,4] In patients with HF, the heart cannot support the body with enough blood and oxygen to ensure systemic metabolism both at rest and during physical activity.[3-5] This results in a restriction of the perfusion of critical organs.[5] Limited cerebral perfusion in these patients can lead to cerebral ischemia and stroke.[5,7] Traditionally, thrombosis, hypoperfusion, and atherosclerosis have been identified as the causes of IS in individuals with HFrEF.[8-10] The two most often identified causes of cardioembolic stroke in people with HFrEF were LV hypokinesia or thrombus formation due to AF.[5,7,8] Virchow's triad (abnormalities of blood flow, vessel wall and blood components), a precondition for thrombogenesis, is unsurprisingly inevitable in patients with HFrEF.[5,8-10] Akinetic ventricular segments, dilated left atrium or ventricle, and decreased blood flow in HF patients may all contribute to increased thrombus formation by a mechanism similar to AF.[7-10] HF patients are in a pro-thrombotic state.[8-10] There is activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, exaggerated inflammation, increased platelet aggregation, elevated von Willebrand factor levels, and impaired fibrinolysis.[5,7] Moreover, HF patients have functional and/or structural damage to blood vessels due to endothelial dysfunction, rheologic changes consistent with increased blood velocity, and atherosclerosis.[8-10] Impaired cerebral autoregulation is another significant condition that accompanies the etiology of stroke.[5,7] Together with all these factors, considering the causal relationship between HF and IS, comparable underlying etiologic risk factors including DM and HT are inevitable for this association.[6-8] As a result of all these aetiological and pathophysiologic mechanisms mentioned above, patients with HF are more susceptible to IS due to large artery atherosclerosis and small vessel occlusion.[5-10]

Due to the variability of HF patient clinical features and the diverse design of published research, epidemiological evidence about the prevalence and incidence of stroke in patients with HF is limited. Nonetheless, HF was thought to be the probable cause of stroke in approximately 9% of all patients.[21,22] According to a recent statement from the population-based, prospective Rotterdam Screening Study, IS was found in 4% of cases during 5 years of follow-up.[10] Other population-based investigations corroborated the Framingham Study's findings, which indicated that people with HF had a 2-3 times greater risk of IS than those without HF.[6-8] Another long-term cohort study described a notable correlation between HF and all stroke subtypes, even after adjustment for a number of different confounders, including AF or atrial flutter.[9] Patients with HF and AF more tended to develop stroke and had a 5-fold escalated risk compared to the general population.8 Despite the paucity of research on the connection between sinus rhythm HF and stroke, two recent population- community-based researches had shown that HF patients were more likely to experience an IS independent of AF compared with the general population.[8,9] During a mean follow-up of 15 months, almost 6% of the participants in this trial experienced an IS. Due to the exclusion of individuals with AF and those using anticoagulants, this incidence is lower than some of the studies described above and higher than others.

Available data on additional parameters of stroke risk in HF patients are based on retrospective cohort studies, post hoc analyses of several large clinical trials and their meta-analyses. Additional risk factors for HF patients were age, LVEF, DM, HT, prior stroke, and AF.[6-8,21-24] Although some evidence suggested that lower LVEF, older age and the presence of AF increase the risk of stroke, not all research revealed this correlation.[8-10,21-24] This shows the need for researches to identify HF patients at high risk for stroke as well as to determine the most appropriate therapeutic strategies for stroke prevention. Age, DM, LA-APD, LVEF, and WBV were found to be independent predictors of IS in this study. The fact that our research cohort included a relatively lower age group compared to previous studies could be the reason why age was a major predictor of IS in contrast to other studies. Due to conflicting data in patients with AF and the current clear recommendations for anticoagulant treatment in AF patients,[3,4,19] the analysis was performed without including AF patients.

WBV is the intrinsic resistance of blood to flow in vessels and is closely pertinent to blood flow velocity.[11,12] Because abnormal blood viscosity reduces tissue perfusion and interacts with other risk parameters, it is a crucial element in the advancement of atherosclerosis.[12,13] Red cell aggregation, haematocrit, plasma viscosity, and red cell deformation are the main determinants that affect blood viscosity.[1,12,13] In everyday practice, measuring and assessing blood viscosity with a viscometer can be challenging and complex. De Simone et al.[11] computed WBV with a straightforward equation using haematocrit and total protein levels and demonstrated the reliability of this formula by performing validation analyses with a viscometer.[12-16] WBV calculated by this formula has been shown to be a good parameter for determining adverse outcomes in many cardiovascular diseases such as stroke, HF, myocardial infarction and coronary slow flow phenomenon.[12-16] Moreover, HCT and plasma protein levels, which were used to calculate WBV, had a well-established association with adverse outcomes

in HF patients.[3,4,25] This study demonstrated that WBV could be a valuable parameter for the prediction of IS in HFrEF patients in sinus rhythm as an additional parameter. For these patients, the management of anticoagulant and antiaggregant therapy may be guided by elevated WBV.

Limitations

The limitations of this study included the retrospective design of our study, the inclusion of a single center and the possible effects of inter-observer variability despite the use of standard diagnostic methods. Nevertheless, the relatively large sample size and the fact that our center was a heart transplant center to which patients from other hospitals and cities were referred made the results of this study significant. Another limitation of the study was that the WBV value was not verified using a viscometer and the temporal variation of WBV was not evaluated. However, further extensive studies have verified the De Simone et al.11 formula and demonstrated that it offers a good substitute for the determination of direct viscosity measurement.

CONCLUSION

WBV is a novel, easily measurable, cost-effective, non-invasive risk marker for the prediction of long-term IS in patients with HF, independent of traditional risk factors. This results underscore the importance of clinical attention to IS risk in patients with HF and highlights the role of WBV as a supplement to potential prevention strategies in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 24.08.2022, Decision No: 266).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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